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Relationship between lactate value and mortality in critical patients diagnosed with diabetic ketoacidosis

Lactate and mortality in diabetic ketoacidosis

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Abstract
Aim: In this study, we aimed to investigate the lactate value and lactate clearance (LC) at the time of presentation to the emergency department and within the first two hours in predicting mortality in patients diagnosed with diabetic ketoacidosis (DKA).
Material and Methods: This retrospectively and observationally planned cohort study was conducted with patients with DKA who presented to the hospital between January 2021 and December 2022. The patients' demographic characteristics, biochemistry, hemogram, and blood gas results at the time of presentation, second-hour lactate value, and outcome parameters were recorded. Then, LC was calculated for each patient. The patients were divided into groups according to the mortality status and the length of hospital stay. The groups were compared in terms of age, blood gas pH, osmolarity, glucose level, lactate level at presentation and at the second hour, LC, and bicarbonate, blood urea nitrogen, potassium levels, length of stay in hospital, intensive care unit admission, inotropic agent requirement, invasive mechanical ventilation requirement and mortality.
Results: The overall mortality rate was 15.6% (16/102). Age, pH, osmolarity, bicarbonate and sodium levels, and second-hour lactate level significantly differed between the groups (Mann-Whitney U test, $p<0.05$). The cut-off and area under the curve values of LC were not significant in predicting mortality ($p>0.05$).
Discussion: Among the patients with DKA who presented to the emergency department, age, the presence of comorbidities, glucose levels at presentation, admission and second-hour lactate values, pH, bicarbonate, potassium, and intensive care unit admission were useful in predicting mortality.

Keywords
Diabetic Ketoacidosis, Lactate, Mortality

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Introduction

The number of patients presenting to emergency departments due to complications related to diabetes mellitus (DM) is currently increasing [1]. According to the data of the World Health Organization, deaths due to diabetes rank 19th globally. In the USA, DM is the eighth cause of mortality [2]. Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are hyperglycemic emergencies with the highest mortality due to diabetes [3]. Rapid diagnosis of these conditions in emergency departments, and the detection and treatment of the underlying causes are essential to reduce the associated mortality.

One of the complications of DM, with which patients usually present to emergency departments is DKA, which is characterized by hyperglycemia, increased anion gap, ketonemia/ketonuria, and metabolic acidosis [4]. DKA is observed in 0.8% of patients with DM and a potentially fatal complication if not recognized and treated quickly [5,6]. Deaths due to DKA have been reported to occur most frequently within the first three days of presentation to the hospital and within the first 48 hours of admission to the intensive care unit (ICU) [7].

Although lactate is mainly produced in muscle cells, it is the end product of an increased anaerobic metabolism when oxygen delivery cannot meet oxygen consumption [8]. Increased lactate levels may be associated with increased production of lactate in diseases that either cause a decrease in oxygen delivery or reduce its elimination, or both in a multifactorial manner [9]. A high lactate concentration associated with a low blood pH value is useful for demonstrating the severity of the mismatch between the supply, demand, and consumption of energy [10]. An elevated blood lactate level is an important finding in the prediction of prognosis in critical diseases [4]. It is frequently detected in both adult and pediatric patients diagnosed with DKA in emergency departments [11,12].

Lactate clearance is the difference between the lactate value taken at a selected time and the first measured lactate value, i.e., the expression of the ratio of the initial lactate value as a percentage [13]. Some studies have underlined the importance of LC measurement in conditions that may lead to hypoperfusion, such as trauma and sepsis [14,15].

In contrast to patients with sepsis, there are limited studies investigating the role of changes in lactate values in patients with DKA in evaluating the severity of clinical cases, response to treatment, intensive care requirement, and prognosis [16,17]. Therefore, the primary aim of this study was to retrospectively investigate the relationship of the lactate values at presentation and LC with mortality in patients who presented to the emergency department with hyperglycemia and were diagnosed with DKA in 2021 and 2022. The secondary aim was to evaluate the relationship of these parameters with the length of hospital and ICU stay, mechanical ventilation requirement, and inotropic agent requirement.

Material and Methods

This research was performed as a retrospective observational cohort study. Approval was obtained from the ethics committee of University of health Sciences, Kartal Dr. Lutfi Kirdar City Hospital (Decision number:2022/514/240/21 Date: 2022-12-28). Patients who presented to the emergency department of the hospital with the diagnosis of DKA from January 1, 2021 to December 31, 2022 were included in the study. The data of the patients were retrospectively screened from the hospital's automation system.

The exclusion criteria were age under 18 years, pregnancy, history of chronic renal failure or a trauma, refusal of treatment or transfer to another healthcare institution due to intensive care requirement, not meeting the American Diabetes Association (ADA) diagnostic criteria for DKA, and having missing or erroneous data. The results of routine blood tests conducted in the emergency department, including hemoglobin, hematocrit, glucose, urea, creatinine, troponin, lactate, bicarbonate (HCO_3-), carbon dioxide, pH, and base excess values were recorded in the form created in the digital environment. In our emergency department, DKA is diagnosed using ADA Guideline I [18]. According to these criteria, DKA is diagnosed based on the presence of a plasma glucose level of >250 mg/dL, arterial pH of <7.3, serum HCO_3- level of <18 mmol/L, and ketone positivity [19]. The patients' admission and second-hour lactate values were used to calculate LC ($lactate_{admission}$ – $lactate_{hour\ 2}$) / lactateadmission x 100) as a percentage. In addition, age, gender, and the presence of comorbidities were recorded. The length of hospital and ICU stay, and discharge and mortality status were also recorded in the form.

Statistical analysis

SPSS, version 25 was used for statistical analyses. For the statistical evaluation, the study data were summarized using descriptive statistical methods (mean, standard deviation, frequency, minimum-maximum values). The Shapiro-Wilk test was used to determine the normality of data distribution for continuous variables. The significance of differences between the mean values was investigated with the two-sample t-test in the case of a normal data distribution, and with the Mann-Whitney U test in the presence of non-normally distributed data. Fisher's exact test was conducted as the independent-samples test of categorical variables.

Receiver operating characteristic (ROC) curve analysis was undertaken to determine the ability of the investigated parameters to predict mortality. The significance level was taken as 0.05 for all tests performed.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The screening of the hospital records revealed a total of 125 patients who were diagnosed with DKA in the emergency department over the study period and underwent blood gas measurements at the time of presentation and at the second hour. However, when the patient records were reviewed, it was determined that 23 patients did not meet the inclusion criteria (nine patients were aged <18 years, 9 were transferred to another hospital with ICU indications, three refused treatment, and two had missing data). After these patients were excluded, the remaining 102 patients were included in the sample. Of these patients, 45 (44.11%) were female and 57 (55.88%) were male. The mean age of the patients was 45.5 ± 21 years. While 48 (47%) of the patients were followed up in the emergency department, 54 (53%) were followed up in the ICU. The mortality rate was 15.6% (16/102 patients). The mortality group had significantly higher values for mean age, glucose and potassium at the time of presentation, and lactate at the first and second hours and a significantly lower pH value at the time of presentation (Mann–Whitney U test, $p< 0.05$) (Table 1). The total length of hospital and ICU stay of the patients was also found to be significantly higher in the mortality group (Table 1). The presence of comorbidities, ICU admission, mechanical ventilation (MV) requirement, and inotropic agent requirement were also significantly higher in the mortality group (Fisher's exact test, $p < 0.05$) (Table 2).

The patients with a hospital stay longer than five days were determined to have lower HCO_3 values and higher blood

Table 1. Distribution of the variables according to the mortality status.

Mortality	Non-mortality group Mean ± SD Median (min-max)	Mortality group Mean ± SD Median (min-max)	p-value
Age	42.85 ± 19.46	66.23 ± 18.53	0.000[1]
	42 (18-88)	74 (30-90)	
Glucose (initial)	475.5 ± 156.34	657.54 ± 183.17	0.002[2]
	464 (211-920)	678 (365-980)	
pH	7.15 ± 0.13	7.09 ± 0.14	0.050[2]
	7.14 (6.85-7.41)	7.10 (6.90-7.27)	
Lactate (hour 1)	3.04 ± 2.05	4.88 ± 2.94	0.024[1]
	2.05 (0.70-14.40)	4.40 (1.70-11.30)	
Lactate (hour 2)	2.11 ± 1.10	4.08 ± 3.49	0.001[1]
	1.90 (0.60-6.00)	3.20 (1.30-14.80)	
Lactate clearance (%)	18.97 ± 42.86	14.51 ± 34.38	0.489[1]
	25.96 (-223.08-83.93)	21.05 (-64.71-53.73)	
Osmolarity	1023.21 ± 7.57	1021.38 ± 8.80	0.251[1]
	1025 (1005-1043)	1018 (1010-1035)	
HCO_3	12.28 ± 5.33	10.42 ± 4.69	0.271[1]
	10.55 (5.40-25.60)	9.30 (5-22.70)	
Blood urea nitrogen	19.18 ± 9.07	43.15 ± 24.77	0.000[1]
	17.50 (3-56)	37 (14-87)	
Sodium	133.39 ± 5.08	131 ± 11.80	0.326[1]
	133 (115-150)	130 (118-159)	
Potassium	4.71 ± 0.83	5.13 ± 0.66	0.050[2]
	4.70 (2.49-7.23)	5.13 (3.59-6.10)	
Base excess	-16.29 ± 7.62	-17.87 ± 7.75	0.422[1]
	-17.80 (-29.70-3.40)	-20.39 (-29.70; -0.70)	
Length of hospital stay (day)	8.56 ± 14.39	13.54 ± 10.02	0.033[1]
	6 (0-125)	12 (1-32)	
Length of ICU stay (day)	3.45 ± 13.05	11.85 ± 10.39	0.000[1]
	0 (0-114)	11 (0-32)	

1: Mann Whitney Test; 2: t-test; SD: standard deviation; HCO_3: bicarbonate; ICU: intensive care unit

Table 2. Results of the independent-samples test of mortality status and other categorical variables.

		Non-mortality n (%)	Mortality n (%)	p-value
Gender	Female	38 (44.2)	8 (46.7)	0.538
	Male	48 (55.8)	8 (53.3)	
Diabetes diagnosis	-	14 (16.3)	0 (0)	0.088
	+	72 (83.7)	100 (100)	
Comorbidity	Absent	39 (45.3)	0 (0)	0.000
	Present	47 (54.7)	100 (100)	
ICU admission	Absent	46 (53.5)	2 (6.7)	0.001
	Present	40 (46.5)	14 (93.3)	
Inotropic agent requirement	Absent	81 (96.4)	2 (15.4)	0.000
	Present	3 (3.6)	11 (84.6)	
MV requirement	Absent	77 (91.7)	1 (7.7)	0.000
	Present	7 (8.3)	12 (92.3)	

ICU: intensive care unit; MV: mechanical ventilation

Table 3. Results of the ROC curve analysis of the study variables in the prediction of mortality.

Variables	Youden index	Diagnostic Values					Roc Curve		
		Cut off	Sensitivity	Specificity	PPV	NPV	AUC	%95 CI	p value
Glucose (initial)	0,362	>676	46,67	89,53	90,5	41,2	0,707	0,61; 0,79	0,007
Ph	0,369	≤7,02	46,67	80,23	29,2	89,6	0,644	0,54; 0,74	0,081
Lactate (hour 1)	0,371	>4,3	53,33	83,72	91	34,8	0,684	0,58; 0,77	0,019
Lactate (hour 2)	0,416	>2,1	80	61,63	94,3	25	0,76	0,67; 0,84	0
BUN	0,44	>31	53,33	90,7	91,8	50	0,801	0,71; 0,87	0
Potassium (K)	0,352	>4,57	93,33	41,86	97,3	21,9	0,68	0,58; 0,77	0,013
Length of hospital stay (day)	0,449	>10	61,54	83,33	93,3	36,4	0,684	0,58; 0,78	0,081
Length of ICU stay (day)	0,555	>8	61,54	93,98	94	61,5	0,815	0,72; 0,89	0
Comorbidity	0,454	>0	100	45,35	100	24,2	0,727	0,63; 0,81	0
ICU admission	0,468	>0	93,33	53,49	97,9	25,9	0,734	0,64; 0,82	0
Inotropic agent requirement	0,81	>0	84,62	96,43	97,6	78,6	0,905	0,83; 0,96	0
MV requirement	0,84	>0	92,31	91,67	98,7	63,2	0,92	0,85; 0,97	0

urea nitrogen (BUN) and base excess values at the time of presentation (Fisher's exact test, $p < 0.05$).

No significant correlation was found between the length of hospital stay and the initial glucose level, admission and second-hour lactate values, and LC. Table 3 presents the results of the ROC curve analysis performed to determine the power and cut-off values of the investigated variables in the prediction of mortality.

According to the p-values of the ROC curve area, all variables except for pH and the length of hospital stay were significant in predicting mortality ($p < 0.05$). The highest Youden index value (the distance from the endpoint of the curve to the left corner on the graph) for the prediction of mortality belonged to MV requirement, followed by inotropic agent requirement. Patients with positive results on mechanical ventilation and inotropic agent requirements in the tests performed based on cut-off values had a higher risk of mortality. The sensitivity rate was observed to be high in the tests performed for the variables of the presence of comorbidities, ICU admission, potassium value, MV requirement, inotropic agent requirement, and second-hour lactate values. In addition to MV and inotropic agent requirements, the length of hospital and ICU stay, and BUN and glucose values also had high specificity values. When all results were evaluated together, it was observed that MV and inotropic agent requirements were the most determinant factors for mortality, followed by the length of ICU stay and BUN and second-hour lactate values.

Discussion

Among the metabolic complications of diabetes, DKA and HHS constitute emergencies with the highest mortality rates [3,18]. In the USA, 220,000 patients were hospitalized due to DKA in 2018, and the mortality rate was approximately 1% [16,17]. Although the mortality rate of DKA is <1% in developed countries, such as the USA and UK, this rate is higher, ranging from 3 to 13% in developing countries [20,21]. Mortality is affected by the adequacy of healthcare services, rapid diagnosis of the condition, and rapid initiation of treatment. The mortality rate of our patients was 15.6%, which is consistent with the literature.

Researchers have focused on the use of various biomarkers in the prediction of mortality. In the current study, we aimed to evaluate the relationship of mortality with the first-hour and second-hour lactate values and LC in patients who presented to the emergency department with DKA. Our study has certain limitations, such as retrospective design and data being obtained from the hospital's automation system. Various drugs and metabolic disorders are known to trigger DKA, and insulin deficiency is the most important cause [22,23]; however, we were not able to access such data through the hospital records. Blood gas analyses in emergency departments are extremely valuable for presenting rapid results and providing important information about the metabolic status of parameters, including lactate, pH, base excess, and HCO_3. Changes in blood lactate values help interpret tissue hypoxia when evaluated together with clinical manifestation and treatment, especially in diseases where perfusion is impaired. According to the Surviving Sepsis Campaign, lactate levels should be monitored to reflect the severity of the disease in sepsis and follow up patients on targeted therapy [15]. DKA is a clinical condition presenting with high lactate levels. In our study, there was a significant correlation between elevated first- and second-hour lactate levels and mortality, which is consistent with the literature [22]. However, lactate values were not significant in determining the length of hospital stay.

Many studies have shown that LC follow-up results in better clinical outcomes [13,23]. According to our findings, LC was lower in the group with a hospital stay of >5 days, although this did not reach a statistically significant level. In some studies, LC has been shown to be significant in predicting 30-day mortality [24]. In our study, no significant correlation was observed between LC and mortality, but LC was lower in the mortality group.

We found that the glucose level at the time of presentation to the emergency department and patient age were significantly associated with mortality. We consider that this may be due to the presence of resistant hyperglycemia and age-related comorbidities. This idea is supported by the literature [3,19]. In clinical practice, especially in emergency departments, rapid, practical, and effective biochemical markers are needed to predict patient prognosis and determine the optimal treatment process. This can reduce mortality metabolic emergencies, such as DKA. We consider that the most effective biochemical and clinical markers will be identified through further studies. In this study, a significant correlation was found between mortality and important parameters for ICU indication, pH, HCO_3, and potassium at the time of presentation ($p < 0.05$). Similar to the studies in the literature [7], the mortality rate was significantly higher in the patients admitted to the ICU. In addition, the presence of comorbidities and inotropic agent and MV requirements were among the significant factors that increased mortality. Glucose value at presentation, patient age, blood gas parameters, severity of metabolic acidosis, course of lactate values from presentation to the second hour, and the length of ICU and hospital were determined to be appropriate and clinically useful diagnostic markers for patients with DKA.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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